Heterotaxia, Congenital Heart Disease, and Primary Ciliary Dyskinesia

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The human heart is strikingly asymmetrical along the left-right body axis. If one begins with the position of the heart in the left chest, continues through asymmetrical venous drainage into the atria and asymmetrical orientation of the 2 anatomically and functionally distinct ventricles, and finally proceeds through the highly asymmetrical coil of semilunar valves and great vessels, the structure and function of the human heart are precisely aligned to the left-right axis. When cardiac asymmetries either fail to develop or align incorrectly relative to each other or relative to other organs, a plethora of congenital heart disease results. This group of heart diseases is called heterotaxy syndrome and represents both a difficult clinical challenge and a fascinating window into the biology underlying one of the most fundamental embryological processes, namely, the mechanism by which an organism establishes the 3 body axes. Positioning of organs along the left-right axis can be divided into 3 broad classes: situs solitus, in which all organs are positioned normally; situs inversus, in which there is mirror image reversal of all organs; and heterotaxy, in which there is any positioning of organs along the left-right axis differing from situs solitus and situs inversus (Figure). Pure situs inversus is found in 1 of 8500 in the general population and is usually not associated with intracardiac defects. In contrast, heterotaxy has a high degree of association with intracardiac defects. It has a reported incidence of 1 of 10 000 and is associated with at least 5% of cases of congenital heart disease.1

Heterotaxy comprises a broad spectrum of abnormalities. In the milder cases there is some left-right asymmetry, which can be discordant from organ to organ or within 1 organ itself. Examples include isolated dextrocardia with abdominal situs solitus and isolated levo-transposition of the great vessels, along with malposition of the great vessels and subpulmonary or aortic obstruction, coexist in the majority of cases. The long-term outcome for patients with isomerism has remained poor despite improvements in the medical and surgical management of other congenital heart disease: the 5-year survival for patients with left atrial isomerism and right atrial isomerism is reported to be only 64% and 29%, respectively.3

Cilia: The Link Between Bronchiectasis, Sinusitis, and Disturbances of Cardiac Laterality

In this issue of Circulation, Kennedy et al4 provide evidence linking human heterotaxy to primary ciliary dyskinesia (PCD). Although this connection has long been suspected on the basis of case reports and animal studies, this is the first systematic study supporting such an association. In 1933, Manes Kartagener, a Professor of Pathology at the University of Zurich, first published on the link between bronchiectasis, sinusitis, and situs inversus. This became known as the “Kartagener triad.”5 Forty years later, Bjorn Afdellius observed that male patients with Kartagener triad had normal-appearing but immotile sperm. These observations led him to the original discovery that abnormalities of the ciliary axoneme were the underlying pathology in Kartagener syndrome and that situs inversus was found in ~50% of patients with immotile cilia.6 PCD is now used to refer to sinopulmonary disease caused by immotile cilia irrespective of the presence or absence of situs inversus.

Cilia are highly conserved organelles found on the surface of almost all cell types. They are microtubule-based structures that usually extend 1 to 15 μm from the apical surface of cells. Recently, cilia have been implicated in a host of biological processes including fluid movement, mechanosensation, signaling, and cell division; ciliary defects underlie a broad spectrum of human disease such as cystic kidney disease, retinal degeneration, and Bardet-Biedl and Meckel-Gruber syndromes.7 Motile cilia are most prominent in the sperm tail and on the epithelia of the respiratory tract and choroid plexus. The motile cilia have a characteristic, highly organized, and chiral microtubule structure, consisting of 9 outer microtubule doublets linked to a central pair of microtubules via radial spokes. Dynein motors connect the outer...
doublets to each other and drive ciliary movement in an ATP-dependent fashion.

Patients with PCD have a wide spectrum of ciliary structural abnormalities, including absence of the outer and/or inner dynein arms or abnormal radial spokes/central apparatus. Mutations in 2 genes encoding outer arm dynein proteins (DNAI1 and DNAH5) are found in \( \approx 35\% \) of patients with PCD.\(^8,9\) The diagnosis of PCD is most commonly made because of bronchiectasis, sinusitis, and male infertility. Although \( \approx 50\% \) of affected patients have situs inversus, cardiac disease has not been commonly thought to be a prominent feature of PCD. Conversely, the respiratory disease sometimes complicating the course of patients with heterotaxy was thought to be primarily secondary to cardiac disease.

What role do cilia play in the development of left-right asymmetry? In his original publication on immotile cilia, Afzelius\(^6\) hypothesized that “cilia on the embryonic epithelia have a certain position and a fixed beat direction, and their beating somehow is instrumental in determining the visceral situs.” However, at the time of the discovery of Afzelius, this was thought to be highly unlikely because embryos were not thought to have cilia. An extensive body of work on mice with ciliary abnormalities subsequently led to the discovery of a ciliary mechanism for the development of left-right asymmetry. Embryos do indeed have cilia; specifically, motile cilia are found on the node (organizer) of most vertebrate embryos, and most other embryonic cells have nonmotile monocilia.\(^10\) Dynein-driven clockwise movement of node cilia generates robust leftward movement of the extraembryonic fluid surrounding the node (nodal flow) at e8.0 of mouse development, corresponding to day 17 of human gestation.\(^11\) Nodal flow triggers a cascade of asymmetrical signals that eventually culminate in normal D-looping of the primitive heart tube and normal asymmetrical cardiac morphogenesis. Mice with absent or paralyzed node cilia have abnormal development of left-right asymmetry. In particular, many mouse cilia mutants have a high incidence of heterotaxy in addition to pure situs inversus. For example, mice with mutations in the axonemal dynein, left-right dynein (lrd), have paralyzed node cilia, and 35\% to 50\% of the embryos have heterotaxy and cardiac defects including complex atrioventricular canal defects, abnormal pulmonary and systemic venous return, and abnormalities of the great vessels, a spectrum of defects that is highly reminiscent of that observed in human heterotaxy.\(^12\) Lrd is not expressed in respiratory epithelia, and therefore lrd mutant mice do not have PCD. Mutation in the dynein heavy chain DNAH5 results in mice with more classic features of PCD, including chronic respiratory infections and randomization of cardiac and visceral situs.\(^13\) Notably, like the lrd\(^{-/-}\) mice, some of the DNAH5\(^{-/-}\) mice also had heterotaxy, again supporting a relationship between PCD and heterotaxy.

**Implications for the Management of Patients With PCD or Heterotaxy**

The finding by Kennedy et al that \( \geq 6\% \) of PCD patients have heterotaxy confirms in humans what the data provided by animal studies have suggested: Motile cilia are required for normal development of left-right asymmetry, and when they are defective, the result is a wide spectrum of cardiac outcomes ranging from situs solitus through heterotaxy to situs inversus. The patients in the present study were all identified because of their respiratory disease, and heterotaxy was identified in a retrospective review of available imaging studies. Because subtle forms of heterotaxy cannot be diagnosed by chest x-ray alone, and only 23\% of the patients with situs solitus, 65\% of the patients with situs inversus, and 76\%
of the patients with heterotaxy in this study had an echocardiogram, it is highly likely that the 6.3% of PCD patients identified with heterotaxy in this study represent an underestimation of the actual incidence of heterotaxy in the PCD population.

From the perspective of the cardiologist, however, these findings also raise the possibility that patients primarily diagnosed with heterotaxy have undiagnosed ciliary defects. Because many heterotaxy patients have a complicated cardiac course including cyanosis, congestive heart failure, and multiple cardiac surgical procedures, pulmonary symptoms are often attributed to their cardiac disease and its treatment. Identification of PCD in the affected patients and subsequent aggressive pulmonary management may contribute to some improvement in outcome for patients with PCD and heterotaxy. In addition, as some heterotaxy patients reach adulthood, identification of an underlying ciliary defect also becomes important as a cause for male infertility. Finally, although only a small number were evaluated, >50% of the patients in this study with both PCD and heterotaxy who were analyzed for mutations in only 2 ciliary genes (DANAI1 and DNAHS5) had identified mutations, supporting a role for genetic evaluation of PCD and heterotaxy patients. It is interesting to speculate that ciliary defects underlie a broader spectrum of congenital heart disease than had previously been suspected. In particular, isolated levo-transposition of the great arteries or complex atrioventricular canal defects are seen in the mouse models of ciliary defects and could very well represent a more subtle form of heterotaxy.

The findings in the report of Kennedy et al encourage a collaborative effort between pulmonologists, cardiologists, and cardiothoracic surgeons to best identify and manage patients with heterotaxy and PCD. The number of heterotaxy patients who actually have a ciliary defect as the cause of their heart disease remains unknown. The data in the current report suggest that a thorough study of the genetics underlying the heterotaxy syndrome may go a long way toward this goal.

Acknowledgments
The author would like to thank George Porter and James Perry for critical review of the manuscript.

Source of Funding
The author’s research is supported by National Institutes of Health (NIH) grant RO1HD045789.

Disclosures
None.

References
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Circulation. 2007;115:2793-2795
doi: 10.1161/CIRCULATIONAHA.107.699256
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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